MASTER'S THESIS

Systematic review of the effects of physical exercise and nutrition interventions on body composition in women with metastatic breast cancer.

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Systematic review of the effects of physical exercise and nutrition interventions on body composition in women with metastatic breast cancer

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Master of Nutrition and Dietetic Practice

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It is my hope that this research will be beneficial, especially to further increase the momentum and direct the future of research in metastatic breast cancer.

1.0 INTRODUCTION

Key Points

1. There is a large body of evidence regarding body composition and interventions with physical exercise and nutrition in early stage (I – III) breast cancer
2. Very little is known about the effects of physical exercise and nutrition on body composition in the metastatic breast cancer (stage IV) population
3. The evidence suggests that body composition is an important prognostic factor in both early stage and metastatic breast cancer

Breast cancer is the most prevalent cancer among women, and due to advances in screening and treatment of cancer, women are now living longer with the disease. Hence, there is a significant population of women worldwide with breast cancer, as well as survivors. It is estimated that one in eight Australian women will develop breast cancer in her lifetime [1]. As a result, health practitioners are more likely to encounter these women on a regular basis. This is also true for women with the incurable form of the disease, metastatic breast cancer. Metastatic breast cancer, classified as stage IV cancer, is the uncontrollable growth of new tissue that starts in a mammary gland and then spreads to other parts of the body [2].

Breast cancer itself, as well as the treatments, can have debilitating effects on the individual and severely reduce quality of life. Some common symptoms include nausea, fatigue, constipation, lack of appetite and nerve pain [3]. Moreover, women diagnosed with breast cancer are prone to psychosocial distress and experience issues with depression, decreased self-esteem and body image [4].

Because of the increased prevalence and survival rates, breast cancer research continues to gain momentum and there is a growing body of research into various aspects of breast cancer treatment and symptom management. It has been discovered that body composition, especially at diagnosis of breast cancer, significantly impacts the effectiveness of treatment and its success in the early stages, I - III [5]. Therefore, women who are overweight or obese i.e. body composition comprises greater fat versus muscle mass, are at higher risk for poor prognosis, reducing prospects for survival. Body composition has a direct impact on decreased time to tumour progression [6] and overall mortality in breast cancer patients [7]. In contrast however, only a few studies around this topic have been conducted in metastatic breast cancer. The treatment for metastatic breast cancer is different to early stage breast cancer, as it would be primarily palliative. There is little known about the impact of this form of the disease on body composition and if these women would derive benefits from interventions with physical exercise and nutrition.

This paper investigates metastatic breast cancer from aetiology and risk factors to the impact on the individual, and reviews the evidence surrounding these issues and their management. It will summarise the clinical trials that have been conducted and the results that can be used to inform practice or provide guidance for this population. It is hoped that this work will bring light to best practice, indicate gaps in the evidence and give direction regarding future research in the area.

2.0 LITERATURE REVIEW

There is still no definitive aetiology for breast cancer, as it can develop when the genetic information the individual's cells carry changes or mutates [8]. How these changes come about and how the cells then develop, depends on many factors in the environment and in the individual and how they impact each other. Some risk factors are modifiable and can be addressed by behaviour change, e.g., physical activity, diet and alcohol consumption. However, some risk factors, e.g., gene mutations, are unavoidable [9].

One of the highest risk factors for breast cancer is family history of the disease [8]. There has been extensive research using breast cancer family data of the BRCA1 and BRCA2 genes. Mutations in these genes confer 10- to 20-fold relative risks to carriers, corresponding to a 30%–60% risk by the age of 60 years [8]. The evidence suggests lifetime risk ratios of 1.8 in families with one affected first-degree relative (i.e., mother, sister, daughter) and it increases approximately two-fold when two first degree relatives are affected [10]. Risk ratios are greatest the younger the age of diagnosis of the first-degree relative.

Specific lifestyle factors, such as exercise and nutritional habits, especially resulting in poor body composition, are associated with an increased risk of developing breast cancer. There is a growing body of epidemiological evidence surrounding post-menopausal obesity and a sedentary lifestyle as important risk factors for breast cancer [11]. Women with lower fat mass or who partake in regular exercise have significantly lower insulin, glucose, and triglyceride levels and higher high-density lipoprotein cholesterol levels. Thus, weight control and physical activity could exert a protective effect against breast cancer through a metabolic pathway [12].

Epidemiological studies have provided clear associations between dietary patterns and breast cancer incidence. A review conducted by Grosso et al (2017) reported an association between high adherence to a healthy dietary pattern and decreased risk of breast cancer. Healthy dietary patterns in this study were consistent with general dietary guidelines, i.e., rich in whole foods (fruit, vegetables, legumes); reduced red meats and processed foods; alcohol consumption equivalent to one serving of wine or beer per day. In contrast, unhealthy dietary patterns were associated with higher body mass index which further increased breast cancer risks.

Furthermore, any alcohol consumption, is associated with increased risk of developing breast cancer [9]. A prospective observational study of 105,986 women enrolled in the Nurses' Health Study, followed up from 1980 until 2008, found that consumption of three to six alcoholic drinks per week was significantly associated with increased breast cancer risk. Cumulative alcohol intake throughout adult life, i.e., consumption both earlier and later in adult life, was independently associated with breast cancer risk [13].

Likewise, exposure to tobacco smoke has been established to provide increased risk of breast cancer for both active and passive smokers. Luo et al (2011) found that active and passive smoking pathologically confirmed invasive breast cancer. The cohort study reported that breast cancer risk increased by 9% between former smokers and non-smokers [14]. Current smokers had an even greater risk at 16% compared to non-smokers. Several cohort studies have identified risk factors involving specific habits of cigarette smoking, which include the duration of smoking, the number of cigarettes smoked, age at initiation, and years of cessation [15]. Xue et al (2011) found breast cancer incidence to be elevated in ever-smokers versus never smokers and the study reported comparable hazard ratios (HR)

between past and current smokers (HR 1.09 versus 1.06, [95% CI], 1.01% - 1.10%), suggesting that cessation had little effect following long-term smoking [16].

Over time, it has been discovered that obesity, defined as abnormal or excessive fat accumulation that presents a risk to health [17], is related to poorer outcomes for women diagnosed with metastatic breast cancer [18]. Obesity at the time of diagnosis is associated with poor prognosis and reduces the rate of survival and the efficacy of the treatment. In 2005, a population-based sample of 1,360 Australian women with breast cancer, found that obesity was associated with distant recurrence of breast cancer, increased mortality from any cause and associated with increased tumour size, and poorer treatment outcomes [19]. Additionally, the literature suggests that breast cancer survivors are at increased risk of obesity and the metabolic syndrome (MetS) and are at a significantly higher risk of developing other chronic diseases such as coronary heart disease [20, 21]. The MetS is characterised by the presence of high serum glucose and triglycerides, low HDL-cholesterol, high blood pressure, and abdominal obesity. Post-menopausal women with MetS are at significantly higher risk (rate ratio 1.58) for breast cancer [22]. Women with low serum HDL-cholesterol and high triglycerides had the strongest association with breast cancer risk.

Peri and postmenopausal women are commonly provided Hormone Therapy (HT) for control of menopausal symptoms [23]. However, the results from the Women's Health Initiative randomised controlled trial comprising over 16,600 women indicated that overall health risks exceeded benefits from the use of HT (combined estrogen plus progestin) over five years [24]. This trial confirmed that HT does increase the risk of incident breast cancer by 53% after use for more than five years. Breast cancer risk also increases based on the length of time of exposure to endogenous estrogen hormones, i.e., early menarche and women who experience menopause after age 55.

Diagnosis

Persons with breast cancer may not be aware of having the disease as they may not present with any symptoms, especially in the early stages of the disease. Consequently, the World Health Organisation (WHO) position paper on mammography screening promotes two early detection strategies for breast cancer; early diagnosis and screening [25]. Early detection is critical to improving breast cancer outcomes and survival. Diagnosis is done via a three-part process; 1. Taking a personal history and a clinical breast examination; 2. Imaging tests (mammogram and/or ultrasound) and 3. A biopsy to remove cells or tissue for examination. In a retrospective study of a population of 2070 women affected by invasive breast cancer, Cedolini et al (2014) found breast cancer screening resulted in significantly higher overall 5-year survival, versus women who had their breast cancer diagnosed by objective physical examination or imaging[26]. Women who had their cancers diagnosed by objective physical examination had a significantly higher prevalence of advanced stage at diagnosis. The result being, significantly higher prevalence of tumour characteristics commonly related to poorer breast cancer prognosis such as greater tumour size and greater lymph node or lymphovascular involvement. Conversely, the patients who were diagnosed via breast cancer screening had a significantly lower prevalence of locoregional and distant recurrences.

Types and Staging of Breast Cancer

Breast cancers are categorised based on their type and staging. Figure I details the eight distinct types of breast cancer. Breast cancers are categorised based on their location in the breast, whether the tumour is invasive or non-invasive, and whether it has spread (metastasized) to the lymph nodes or other parts of the body [26].

Figure 1 – Types of Breast Cancer[1]

Location	*Description*
Ductal carcinoma (DCIS)	non-invasive breast cancer that is confined to the ducts of the breast
Lobular carcinoma (LCIS)	a non-invasive breast cancer that is confined to the lobules of the breast
Early breast cancer	invasive breast cancer that is contained in the breast and may or may not have spread to lymph nodes in the breast or armpit.
Paget's disease of the nipple	a rare form of breast cancer that affects the nipple and the area around the nipple (the areola), and is commonly associated with an invasive cancer elsewhere in the breast
Inflammatory breast cancer	a rare form of invasive breast cancer that affects the lymphatic vessels in the skin of the breast, causing the breast to become red and inflamed
Locally advanced breast cancer	an invasive breast cancer that has spread to areas near the breast, such as the chest wall
Metastatic breast cancer / advanced breast cancer	invasive breast cancer that has spread from the breast to other parts of the body

Breast cancer is staged according to the American Joint Committee on Cancer (AJCC) TNM system, which is based on three factors: 1. The size or diameter of the breast tumor (T) and it if has grown into nearby areas; 2. If the cancer has spread to nearby lymph nodes (N) and 3. Whether it exhibits invasive characteristics i.e., the cancer has metastasized or spread to other parts of the body (M) [27]. Appendix 1 lists the types of tests that are commonly used in diagnosis and staging of the disease. The earliest stage cancers are called stage 0 and then range from stages I to IV. The lower the number indicates the less the cancer has spread. Appendix 2 describes the stages of cancer.

[1] Australian Government. Types of breast cancer | Breast cancer. 2015 2015-12-18T09:00+11:00 [cited 2017 November 17]; Available from: https://breast-cancer.canceraustralia.gov.au/types.

Types of Treatment

Anti-cancer treatment may be for curative or palliative intent depending on the type and staging of the disease. Adjuvant therapy has a curative intent and is customarily used following primary radical treatment to reduce the risk of cancer recurrence. Adjuvant therapies are well-established forms of treatment for common malignancies such as breast cancer. These include hormone therapies, chemotherapy (systemic therapy targeting micro-metastases) and radiation therapy (local tumour control) and can be given individually or combined [28]. Neo-adjuvant therapy refers to therapy given before the primary treatment and it is also applied as part of curative treatment. It may be used to reduce large tumors, which may aid in surgery. It may be important for some patients to avoid the treatment delay caused by surgery and recovery and as such neo-adjuvant therapy is utilised to treat both the primary tumour and potential micro-metastases [28]. The appropriate treatment protocol must be ascertained for each patient, as metastatic breast cancer has unpredictable clinical behaviour and is subject to biological heterogeneity [29].

Palliative care is offered to patients with metastatic cancers. The WHO definition of palliative care is, “an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual” [30]. Palliative care is therefore multi-modal, and early initiation has been found to have beneficial effects for both patients, their families and the healthcare system [31]. The literature suggests improvement in symptoms such as depression, reduced aggressive care at the end of life, increased advanced directives, improved patient and caregiver quality of life, reduced hospital length of stay and hospitalizations, and reduction in the medical cost of care [31].

Cancer-related Malnutrition

The nutritional status of patients with cancer has a significant impact on their treatment outcome. The aetiology of malnutrition in patients with cancer is multifactorial [32] and can result from the systemic effects and/or the local effects of the tumor, or the side effects of anti-cancer treatment [33]. Cancer-related malnutrition occurs because of an imbalance between the increased nutritional needs of the patient, the demands of the tumor and the availability of nutrients in the body [32]. Additionally, malnutrition can present in both overweight and underweight individuals. Cancer cachexia, a specific form of malnutrition, can result from prolonged undernutrition and is characterised by systemic inflammation, progressive, involuntary weight loss with depletion of lean body mass, muscle wasting and weakness, oedema, impaired immune responses, and declines in motor and mental function [32, 34]. Cachexia also significantly increases the risk of death and is one of the primary causes of death in cancer [35]. Notably, patients with metastatic disease are at significantly increased risk of malnutrition [33, 36]. Hebuterne et al (2014) found the prevalence of malnutrition in women with breast cancer to be approximately 20 percent and even greater likelihood in metastatic breast cancer with an odds ratio of 2.97 (95% CI: 2.14-4.12).

It is established that risk of sarcopenia increases in breast cancer patients undergoing chemotherapy or androgen therapy [37]. Sarcopenia is a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death [38]. There is now increasing evidence that weight gain in breast cancer patients consists almost

entirely of increased adipose tissue with no gain, or even loss, of lean tissue. This mechanism is called 'sarcopenic' obesity [39]. Consequently, there is reduced muscular strength and increased muscular dysfunction. The literature indicates that muscle wasting is frequently observed in normal, overweight or even obese cancer patients [40]. As such, a decrease in skeletal muscle mass can often be masked by excess fat mass. Sarcopenia, which encompasses a low amount of muscle mass and relatively high amount of fat mass, is a major physical issue that presents in women with metastatic breast cancer [5, 41, 42]. This can be due to the disease, the age of the individual at diagnosis and because of treatment, for instance, hormonal treatment impacting on fat metabolism and resulting in fat deposition [43].

It therefore stands to reason that poor body composition metrics are inversely related to treatment tolerance. Shachar et al (2017) found that patients with low skeletal muscle index and low lean body mass developed grade 3/4 toxicity (relative risk 1.29 and 1.48; P=0.02, respectively), which was significantly higher than toxicity levels experienced by those with a greater skeletal muscle index [44]. Increased incidence and severity of treatment-related toxicity have also been exhibited in malnourished patients compared with those patients with normal, stable weight [45]. It was determined that the occurrence of muscle wasting is a significant predictor of toxicity and time to tumour progression (TTP) in metastatic breast cancer patients treated with chemotherapy. Toxicity was found in fifty percent of the sarcopenic patients in this study versus twenty percent in the non-sarcopenic patients [45]. Therefore, it is imperative that the individual with breast cancer limit the loss of muscle mass after diagnosis [46].

There has been extensive research regarding physical exercise interventions to maintain muscle mass, fitness and quality of life during cancer treatment for patients with early-stage cancers [47]. Physical exercise is an effective intervention to improve cardiorespiratory fitness, physical functioning and overall quality of life in breast cancer patients and survivors [48]. Individuals with higher muscle mass have greater ability to tolerate chemotherapy and have better survival rates [49]. Ballard-Barbash et al (2012) reported in their systematic review that there was consistent evidence that high levels of daily physical activity are associated with reduced all-cause, breast cancer-specific mortality. Overall, the current literature indicates that supervised exercise therapy, in both aerobic and resistance training, was found to be safe, feasible and positively associated with decreased fatigue and improved fitness, in patients with early-stage breast cancer receiving conventional cytotoxic adjuvant therapy versus usual care [50]. Resistance exercise has been shown to be effective in maintaining muscle mass and aerobic training effective in reducing fat mass, in patients with early-stage breast cancer [51].

Nutrition

Individualized nutritional support is an essential part of the multi-modal approach for the care of cancer patients [52]. It has been established that cancer cachexia is a progressive wasting disease that cannot be fully reversed by conventional nutrition support [53]. Therefore, early initiation of nutrition intervention is highly recommended. As previously discussed, muscle wastage and weight loss are critical issues for cancer patients. Early recognition and treatment of the nutritional and metabolic alterations occurring during cancer are critical [38]. As such, adequate nutritional support should be provided to minimize sarcopenia or wasting [52].

Research has indicated the advantages of various nutritional interventions in maintaining appropriate nutritional status and body composition during breast cancer treatment. In this regard, the ESPEN guidelines on nutrition in cancer patients recommends consumption of 1-1.5 g/kg protein per day, as the increased protein intake promotes muscle protein anabolism [54]. Likewise, omega-3 polyunsaturated fatty acids, in doses of at least 1.5 g/day of EPA for a prolonged time to advanced cancer patients experiencing weight loss, has been found to be useful in the modulation of metabolic changes and associated with improvement of clinical, biological and functional parameters and may help reduce muscle wasting [55]. Several research groups have conducted studies surrounding the efficacy of docosahexaenoic acid (DHA) which is an omega-3 polyunsaturated fatty acid of marine algal origin and provided by the diet. The results suggest that DHA can increase the efficacy of anti-cancer treatments by increasing tumour sensitivity to chemotherapy, while not affecting non-tumour tissues [56]. Consequently, this is particularly beneficial for patients with metastatic disease.

Conclusion

Physical activity and nutrition are essential factors during breast cancer survivorship which impacts on body composition, cancer recurrence, and quality of life. The growing body of evidence surrounding the effectiveness of physical exercise and nutrition for maintaining appropriate body composition in non-metastatic cancer patients is compelling. Despite this, very little research has been conducted on the effects of physical exercise combined with nutrition interventions in women with metastatic breast cancer.

It is evident that more women are living longer post diagnosis of metastatic breast cancer. Therefore, this systematic review was conducted to investigate the impact of

interventions with physical exercise and nutrition on body composition in women with metastatic breast cancer. The results are discussed in the next chapter.

3.0 SYSTEMATIC LITERATURE REVIEW

Systematic review of the effects of physical exercise and nutrition interventions on body composition in women with metastatic breast cancer

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CI and BM conceptualised, designed the study and prepared the protocol. CI and AB conducted initial and full text reviews and appraised the studies. CI prepared the manuscript and BM provided methodological expertise and revised the drafted manuscript.

ABSTRACT

Purpose

Breast cancer is one of the most common types of cancer in women. In metastatic breast cancer, quality of life is essential and directly associated with body composition. This review aims to evaluate the evidence for physical exercise intervention and/or nutrition intervention on body composition in women with metastatic breast cancer. Secondary outcomes of interest are fatigue, quality of life, survival, toxicity, and depression.

Methods

Pubmed, CINAHL, Cochrane Central and EMBASE databases were searched from database inception to October 25th, 2017, using key words and controlled vocabulary. All studies that investigated the effect of physical exercise and nutrition interventions in adult women with metastatic breast cancer were included.

Results

No studies were identified that investigated the effects of exercise and / or nutrition interventions on body composition in this population. Seven studies reported positive results of physical exercise interventions on the secondary outcomes of fatigue, quality of life and survival. These studies had low statistical power as they had small sample sizes.

Conclusions

There is insufficient evidence to draw a positive conclusion regarding the impact of physical exercise or nutrition in women with metastatic breast cancer. There is a cautious indication that physical exercise at least does no harm to patients with metastatic breast cancer. Further trials with robust study designs are needed.

Key words

Metastatic breast cancer, physical exercise, nutrition, body composition, fatigue, quality of life

INTRODUCTION

Although breast cancer is the most common cancer among women in the world (25% of all cancers), it has a high survival rate when detected and treated early [57, 58]. Survival rates continue to improve due to advances in cancer prevention, diagnosis, and treatment [59]. In Australia, the overall five-year survival rate for breast cancer in females is 90% and if the cancer is limited to the breast, the five-year survival rate increases to 96% [1]. Early detection, which involves screening and early diagnosis, is crucial to ensure that appropriate treatment is commenced promptly.

Despite treatment advances, there is a growing number of women who develop metastatic breast cancer, where the cancer spreads beyond the primary site of the breast to other parts of the body. This is also called 'advanced' or 'stage IV' breast cancer [26]. Metastatic breast cancer is virtually incurable and is the cause of death for women who die from breast cancer. In developed countries like Australia, approximately 20 to 30% of women with breast cancer are likely to be diagnosed with stage IV breast cancer [60], where treatment options are primarily palliative, or not for curative intent [61]. Although the five-year survival rate for this population of women is presently 40%, it has been increasing over time and indicates that more women are living longer with metastatic breast cancer.

Inherent with a diagnosis of breast cancer are adverse side effects. Common symptoms that accompany breast cancer treatment include psychosocial distress, typically anxiety and depression [62, 63]. About one-third of women are severely impacted and these symptoms can persist for years [64]. Additionally, cancer-related fatigue is experienced by 80 – 100% of women with breast cancer during chemotherapy [65]. Another important symptom of breast cancer treatment is involuntary weight gain. Recent studies

have reported that the prevalence is approximately 35 -85% of patients with breast cancer [66, 67]. Women with breast cancer undergoing chemotherapy or androgen therapy are also at an increased risk of sarcopenia [37], i.e. a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength [38]. Consequently, these symptoms can have debilitating effects on physical functioning and quality of life.

It has been discovered that in early-stage breast cancer, body composition is a determinant of improved prognosis for the patient [49]. Individuals with cancer that have a relatively high muscle mass have a greater ability to tolerate chemotherapy and have better survival rates than individuals with a relatively low muscle mass [49]. There is a large body of evidence regarding the effects of physical exercise and nutrition intervention on body composition and hence weight management, sarcopenia and other common symptoms, in women with early stage (I – III) breast cancer. Resistance exercise has been indicated to help reverse the effects of sarcopenia during adjuvant chemotherapy [5]. Physical exercise is an effective intervention to improve body composition, cardiorespiratory fitness, physical functioning, fatigue and overall quality of life in early breast cancer patients and survivors [48]. Ballard-Barbash et al (2012) reported in their systematic review that there was consistent evidence that physical activity is associated with reduced all-cause and breast cancer-specific mortality [68].

In addition to physical exercise, nutrition is a key component in ensuring appropriate body composition is maintained. There is evidence that dietary protein in conjunction with physical exercise, enhances muscle growth and prevents muscle loss in patients with age-related sarcopenia [69]. However, in cancer patients, standard interventions are not sufficient to reverse the impact of the systemic, metabolic syndrome of muscle loss and

wasting due to the disease [70, 71]. Due to these metabolic alterations resulting in physical inactivity, low dietary intake and potential anabolic resistance, the situation in cancer care is even more challenging. It is compounded by the fact that the feasibility and effect of physical exercise and nutrition interventions have not been sufficiently investigated in metastatic breast cancer yet.

Objective

This systematic review aims to evaluate the evidence for physical exercise intervention and/or nutritional intervention on the primary outcome of body composition in adult women with metastatic breast cancer receiving any treatment, versus no treatment. Secondary outcomes of interest are fatigue, quality of life, survival, toxicity, and depression.

METHODS

The study was registered in the PROSPERO database and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [72].

Search Terms

Electronic searches were conducted in the Pubmed, CINAHL, Cochrane Central and EMBASE databases up to October 25, 2017. Database searches included predefined key terms and no automatic filters were used. The studies that were identified from the databases were saved and managed in Covidence [73], a platform created by Cochrane for systematic reviews. Numbers were recorded and reported in a PRISMA flowchart (Figure 1). Appendix 3 describes the complete search terms which included:

Stage IV OR metastatic OR “Stage four” AND

Breast OR Mammalia* AND

Malignan* OR Neoplas* OR Tumour* OR cancer* OR carcinoma* AND

Protein OR “amino acid” AND

Supplement* OR nutrition* OR diet* OR "Fatty Acids, Omega-3+" OR “Fish Oils” OR "n-3 polyunsaturated" OR “Eicosapentaenoic Acid*” OR “Docosahexaenoic acid*” OR

“Physical activity” OR Exercise OR “resistance training” OR cardiovascular OR exercise OR Yoga OR Pilates OR hydrotherapy OR aerobic* OR "Therapeutic Exercise"

Eligibility criteria

This review initially aimed to include only RCTs, but after the initial and full-text screening revealed only two RCTs on this topic it was subsequently expanded to include all prospective studies that measured the effects of physical exercise and/or nutrition interventions versus a control, usual care or no intervention. The primary outcome was body composition, however, studies that did not report body composition were eligible if reporting any of the secondary outcomes of interest, which were fatigue, quality of life, survival, toxicity or depression.

The population being investigated was adult women 18 years and over who were diagnosed with stage IV or metastatic breast cancer, undergoing any kind of treatment including chemo and / or radiation therapy, hormone therapy and palliative care or no treatment. Studies with any physical activity and / or nutrition intervention with a minimum duration of 4 weeks were included. Studies were only eligible if written in the English language.

Exclusion criteria

Studies that did not report comprehensive results (e.g. study protocols or conference abstracts) were excluded, and studies that did not have any full text online or library access were excluded.

Data Management

The studies located from the electronic database searches were imported into the Covidence platform [73]. Two independent reviewers (CI and AB) conducted initial screening

for relevance, based on the titles and abstracts. Conflicts were resolved by the third reviewer (BM). When necessary, full text papers were used to determine if the study met the criteria. Where full text publications/papers were not available, the authors were contacted via email requesting access to the results or the full text paper.

Assessment of Risk of Bias in included studies

1. The risk of bias of the included studies was assessed by using The Downs and Black evaluation tool [74] by CI as the first assessor and AB and BM as second assessors. Conflicts were resolved by BM, where applicable. The Downs and Black evaluation tool is validated to judge the quality of both randomized and non-randomized study designs. Each study was assigned a grade of low, medium or high risk of bias, based on each of the following parameters; 1. Reporting bias, 2. External validity, 3. Internal validity, 4. Selection bias 5. Power.

RESULTS

The electronic database searches identified 3420 potentially relevant studies summarised in Figure 1. After removal of duplicates and initial screening sixty-two studies were discovered for full text screening. However, only abstracts could be located for six of the studies. Following several failed attempts to contact the authors, five studies were excluded due to inability to determine relevance to the review and one study is ongoing, hence no results were available. After full-text screening, seven studies conformed to the inclusion criteria, featuring two RCTs and one quasi RCT, and were eligible for the review.

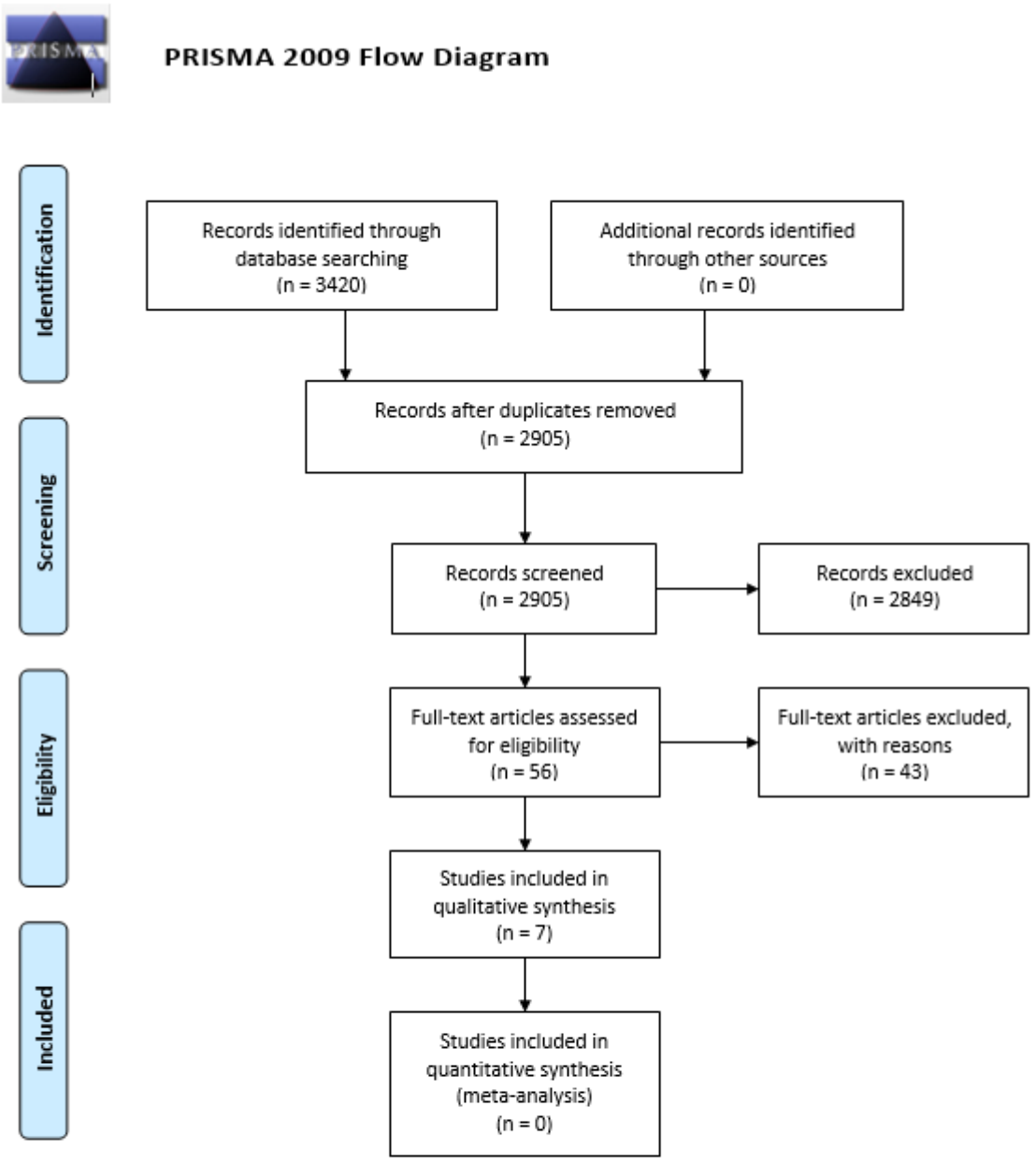
The final selection of seven studies comprised a total of 348 women with metastatic

breast cancer. There was high heterogeneity regarding study designs and outcomes, as all had different interventions and outcome parameters. All studies had a form of physical activity [75-81] and one study had a physical exercise and nutrition component [75]. Two studies investigated the effects of yoga on fatigue [77, 80]. One study intervened with gentle seated exercise, another used moderate intensity exercise and one study was a case report using a combination of various exercises. The Block Centre [75] employed a holistic approach to cancer care including strength, endurance and range of motion exercises. Yee et al (2014) explored the difference in physical activity levels between women with metastatic breast cancer living in the community versus their healthy counterparts.

None of the studies reported on the primary outcome of body composition. Three studies reported on fatigue. However, meta-analysis could not be performed as the studies were too diverse in study design and handling of control groups. Additionally, different measurement tools and statistical tests were employed; results were not reported in any standardized manner, and missing data prevented meaningful meta-analysis. Table 1 summarises the design of the seven included studies.

Figure 1 – PRISMA Flowchart

PRISMA Flowchart



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.* PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Table 1 – Summary of interventions and outcome measures

Study	*Intervention (duration/frequency)*	*Control*	*Outcome measure of interest*
Ligibel, 2016	Moderate intensity exercise Duration – 16 weeks Frequency – 150 minutes/ week	Wait list	• Physical functioning – EORTC QLQ-C30 • Fatigue - Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue • QoL - EORTC QLQ-C30
Vadiraja, 2017	Yoga Duration – 3 months Frequency – 24 sessions	Supportive therapy and education	• Fatigue severity and Frequency – Fatigue Symptom Inventory
Headley, 2004	Seated exercise Duration – 4 cycles of chemotherapy Frequency – x 3/week	Continued usual physical activities	• Fatigue and QOL – Functional Assessment of Chronic Illness Therapy–Fatigue Version IV (FACIT–F)
Block, 2009	Interval and endurance training, strength training therapeutic Yoga, Pilates and Qi gong Duration – Ongoing	None	• Survival – months
Carson, 2007	Yoga Duration – 8 weeks Frequency – Daily	None	• Fatigue – daily diary logs
Yee, 2014	Average steps / day Time spent in moderate-to-vigorous intensity physical activity Duration – 7 days Frequency – no intervention	Healthy women in community	• Fatigue - FACIT-F
Born, 2010	Resistance training, mobility, coordination, ball/stick skills, cardiovascular training Duration – 9 weeks Frequency – once/week	None	• Exercise capacity – 6 min walk test • QoL – RAND-36 questionnaire

Quality Analysis

Risk of bias

Table 2 summarises the Downs and Black domains and the results of how each study was assessed. The high heterogeneity of the studies was clear in the assessment of risk of bias. The studies used varied designs, some randomized and non-randomized, and with or without a control arm, which directly impacts risk of bias. According to the risk of bias assessment by the Downs and Black evaluation tool, most of the studies scored between 17 – 27 out of a maximum of 32 points. Due to the diversity of the studies, there were some parameters within the domains of the tool that were not applicable to all the studies. However, most were judged as having a low to medium risk of bias for all parameters, except for the Yee et al (2014) and Born et al studies which were judged to have a higher risk of bias. Risk of bias was negatively affected when studies relied on patient self-report or subjective data. Although there were small sample sizes, six of the studies were awarded maximum points for power. As it is impossible to blind participants to an exercise intervention, studies were not excluded when judged high risk of bias in this domain. Instead, each study was judged on its merit according to each parameter.

Table 2 – Risk of Bias of included studies as assessed by the Downs and Black Risk of Bias Tool

Summary Table - Risk of Bias						
Author, year	*Reporting Bias*	*External Validity*	*Internal Validity*	*Internal Validity (selection bias)*	*Power*	*Notes*
Ligibel, 2016	Low	Low	Medium	Low	Low	· n = 76 · RCT - moderate intensity exercise · High attrition rate. · Self-report data collected
Vadiraja, 2017	Medium	Medium	Medium	Low	Low	· n = 65 · RCT - Yoga vs supportive counseling intervention · Unable to blind subjects
Headley, 2004	Low	Medium	Medium	Low	Low	· n = 32 · Quasi RCT - seated exercise intervention · Low self-report data collected
Block, 2009	Low	Low	Medium	Medium	Low	· n = 90 · Observation study · Integrated care (nutrition, exercise, mind-spirit) vs usual care · Survival data
Carson, 2007	Low	Low	Medium	Medium	Low	· n = 13 · Feasibility pilot study · Yoga-based program · Small sample size
Yee, 2014	Low	Low	Medium	High	Low	· n = 71 · No intervention · MBC patients vs healthy population · No confounders reported
Born, 2010	Medium	High	Medium	Medium	High	· n = 1 · Individual case report · Low power

Outcome Measures

Although the included studies involved interventions with physical exercise and / or nutrition, none of the studies assessed body composition as an outcome. The included studies reported on the secondary outcomes of interest for this review: fatigue, quality of life and survival. The most common outcomes for these studies were fatigue (5 studies) and quality of life (3 studies). Exercise capacity (2 studies), physical functioning (1 study), survival (1 study) and muscle strength (1 study) were the other outcomes of interest. There were four tools employed in the studies to measure fatigue and three questionnaires to measure quality of life (Table 1). Quality of life (QoL) encompasses various aspects of life and is measured over several subjective and objective domains. These instruments are all validated tools commonly used in the assessment of QoL in cancer patients. The customary domains include functioning (e.g., physical, cognitive, emotional) and symptoms (e.g., fatigue, pain, dyspnea).

Interventions

Block et al (2009) is an observational case series that reported on the BCICT whose integrated cancer treatment program incorporated physical exercise and a nutrition component consisting of personalized nutrition and a supplement regimen. This was the only study with a nutrition component, however, there were no results reported on the specific effects of the nutrition intervention. The other studies included Yoga, and various combinations of aerobic and or resistance exercise interventions, which differed in mode, timing and intensity. Table 3 summarises the designs and findings of the studies.

Effects of Interventions

Fatigue

Of the seven studies, five reported on fatigue as an outcome and of those, three investigated a yoga intervention and two employed moderate intensity exercises. The Carson et al (2007) study findings suggest that patients who practiced Yoga longer on a given day were more likely to experience lower levels of fatigue and that the positive effects of Yoga were indicated to continue the day after exercise. Yoga was also used by Vadiraja et al (2017) in their exercise arm. They report between group analysis that their intervention group experienced better decrease in fatigue severity and frequency compared to the control group with over 61% and 64% respective change from baseline between comparators. Within group analysis also indicated a significant decrease in fatigue severity and frequency. Similarly, in Headley et al (2004) the intervention group participating in seated exercise experienced less increase in fatigue and slower decrease in physical QoL compared to a control (usual activities). Fatigue scores saw a reduction from 77% to 56% of maximum, over the duration of the intervention [78]. Another study indicated no significant difference between the intervention group employing moderate intensity exercise versus the wait list control group [79]. However, there was a high attrition rate (23%) in the intervention arm versus control. The community-dwelling subjects with metastatic breast cancer group indicated higher levels of fatigue (X = 38.0 (9.8) versus their control group healthy counterparts (X = 46.3 (4.6) in the Yee et al (2014) study [81]. Overall, the studies indicated the positive impact of physical exercise on fatigue. However, due to the low sample size, the statistical power of these results is low.

Table 3 – Summary of Study designs and Findings of the 7 included studies

Study Size and Design	Data			Findings
Ligibel, 2016 n=76 Randomised control trial		**Exercise (Standard Deviation)[2]**	**Control (Standard Deviation)**	• Nonsignificant improvement in physical functioning in intervention vs controls at 16 weeks • Participants in intervention group reported non-significant improvements in global QoL • No significant differences noted for fatigue and exercise self-efficacy in intervention vs control • Moderate intensity physical activity is safe for women with metastatic breast cancer (MBC) • ~70% of intervention group completed the exercise program vs 84% of control group
	QoL (EORTC QLQ-30)[3] Baseline	67.2 (19.4)	71.5 (20.2)	
	Change from baseline	6.0 (17.5)	-1.0 (21.5)	
	Fatigue (FACIT-F)[4] Baseline	37 (10.8)	36 (10.3)	
	Change from baseline	2.7 (8.4)	2.7 (9.3)	
Vadiraja, 2017 n=65 2-arm randomised control trial	Fatigue Symptom[5] Inventory	**Baseline Yoga (SD)**	**Post Yoga (SD)**	• Significant differences noted between groups • Better decrease in fatigue severity in Yoga compared to control group • Better decrease in fatigue frequency in Yoga compared to control group
	Fatigue severity	17.1 (9.4)	6.7 (7.1)	
	Fatigue frequency	8.7 (4.8)	3.7 (4.0)	

[2] Standard deviation if reported in the study
[3] Scores 0 -100. Higher score means higher response level
[4] Higher score means better QoL
[5] Higher score means more fatigue

Study Size and Design	Data Mean (SD)			Findings
Headley, 2004 n=32 Quasi-experimental pilot study with randomised trial	Combined (Intervention + Control)	**Baseline**	**Post**	• Fatigue increases in women with MBC as chemotherapy cycles progress • Intervention group experienced less increase in fatigue and slower decrease in physical QoL vs. control • Spousal support in intervention group possible confounder
	FACIT-F	120.6 (22.8)	99.6 (29.5)	
Block, 2009 n=90 Consecutive case series	Survival rate	**BCICT**	**Comparable MBC group**	• BCICT group survival rate approximately double that of comparison groups • Substantially more favourable survival rate for MBC patients undergoing comprehensive or integrative cancer care • Survival of BCICT prognostic subgroups longer than those of the comparator populations
	Median survival	38 months	20 months	
	3-years survival 5-years survival	52% 27%	- 17%	
	Diagnosis after 1990	32 months	15.8 months	
Carson, 2007 n=13 Pilot study	Daily diary log (P <0.01)	**Beta score**[6]	**t-score**[7]	• Yoga practice resulted in lower pain and fatigue in MBC patients • Positive effects of Yoga practice carried over to the next day
	Fatigue (baseline intercept)	46.7	11.8	
	Treatment time	-3.29	-1.45	

[6] Regression analysis indicating an inverse relationship between increased Yoga practice and decreased fatigue
[7] Used to determine if the null hypothesis is correct i.e., Yoga more effective

Study Size and Design	Data			Findings
Yee, 2014 n=71 Observation study		**MBC group (SD)**	**Healthy group (SD)**	• Fatigue significantly higher in MBC group vs. healthy group • The women with MBC were significantly less active • MBC group spent significantly lower duration engaged in moderate to vigorous physical activity • MBC group had significantly lower estimated VO_2max vs. healthy women • MBC group significantly weaker - absolute and relative strength measures
	FACIT-F	38.0 (9.8)	46.3 (4.6)	
	EORTC QLQ-30	70.8 (20.4)	81.7 (15.0)	
Born, 2010 n=1 Case report		**Baseline**	**Post**	• Self-report QoL – improvement in social functioning and vitality • Physical functioning, role limitation and health change - unchanged • Clinically relevant improvement in 6-minute walk test - exercise capacity • Attention patient received may be a confounder
	RAND-36 QLQ	10	20	

Quality of life

Three studies investigated QoL as an outcome. Ligibel et al (2016) reported that participants in the intervention group (moderate exercise) reported nonsignificant improvements in global QoL. Headley et al (2004) reported that the intervention group (seated exercise) experienced a slower decrease in physical quality of life versus the control group with successive chemotherapy cycles. The study also reported that the women in the intervention group were significantly more likely to have spousal support. Born et al (2010) reported on an individual case study where a clinically relevant improvement in social functioning and vitality was indicated after an exercise intervention using combination aerobic and resistance training. In conclusion, the studies generally observed an improvement in QoL in patients who participated in a physical exercise intervention.

Survival

Only one study investigated survival as an outcome [75]. This study was a case series comparing the length of survival of patients, diagnosed before 1998, at the BCICT, versus comparable metastatic breast cancer populations in published studies [82, 83]. The BCICT patients employing both conventional and complementary therapies, had significantly more favourable survival outcomes than their comparators. It was noted that survival was the longest in the most recent cohort receiving taxane therapy – post 1990, (used in breast metastatic cancer) compared to other cohorts. The survival time was approximately double or higher that of comparable populations, despite having patients with worse prognoses. For the BCICT, the median survival time from metastasis was 38 months, versus 20 and 23 months for the Anderson and Clarke studies; 3-year survival was 52% and 5-year survival

was 27% versus 17% reported by Anderson et al (2000). The authors concluded that the results of the comprehensive approach to treatment by the BCICT was indicative of considerably more favourable survival outcomes for metastatic breast cancer patients.

DISCUSSION

This systematic review provides an overview of the available studies that have investigated the effects of physical exercise and nutrition interventions on body composition, fatigue, QoL and survival in patients with metastatic breast cancer. Our findings indicate that only three small RCTs in patients with metastatic breast cancer applying an exercise intervention have been conducted, and no studies have investigated the combined effects of physical exercise and nutrition, nor nutrition interventions only. The effect on body composition could not be evaluated as none of the studies reported on this outcome. This is a major gap in the literature. Moreover, the studies are very heterogenous, with incongruent methods of reporting, making it impossible to meta-analyse the results on fatigue, QoL or survival.

Based on our findings, there is a cautious indication that exercise at least does not worsen fatigue, quality of life or survival and two RCTs with a minimum intervention of twelve weeks found a beneficial effect on fatigue. In summary, improvements in reported fatigue levels were noted in patients who participated in an exercise intervention, or were more physically active, as compared to control patients or those who were less physically active [78, 80].

Limitations of the review and included studies

Given the upcoming/rising number of people living with metastatic breast cancer and the scarcity of physical exercise and nutrition research in advanced disease, it was essential to explore studies conducted in this population. The effects of the interventions in women undergoing active treatment for curative intent would be different to that of the

metastatic population, which would primarily be palliative. Therefore, the current results are translatable to the population of women with metastatic breast cancer, but caution must be exercised as the individual studies lack statistical power due to small sample sizes and, in one case, high attrition. Furthermore, the available studies had a considerable degree of heterogeneity between studies as to mode, frequency and intensity of exercise, treatment of control arms and method of reporting the data.

RCTs are considered the gold standard in research as they aim to reduce overall bias and determine if and how a therapeutic intervention works, and whether results can be generalised to the population in question. Only two RCTs and one quasi-RCT qualified for inclusion in this review [78-80]. Of these, one was an experimental pilot study, and another had two intervention arms (exercise versus counseling). Another three studies did not have a control arm and randomization was not applicable [75-77], and the final study was an individual case [76]. As a result, of the diversity in structure, intervention and design, it was impossible to compare the studies to determine the prognostic effects or efficacy of interventions.

Another limitation to the review resulted from the inclusion of studies that rely on patient self-report data, which are highly subjective and lead to inherent increased risk of bias regarding the measurement and significance of the outcome [78, 79]. One study reported nonsignificant results, which could have been affected by a very high attrition rate in the intervention arm [79]. Subjective data and high attrition rates negatively impact the robustness of the results from these studies. While some studies accounted for possible confounders, this was not the case for all. Spousal support [78] as well as attention received during the intervention [76] were indicated as confounding factors in two of the studies. The

other studies either did not account for confounding or reported intent to treat or covariate analysis. This compounded the fact that the studies had low statistical power due to small samples and further reduced the ability of the review to determine what, if any, inferences can be drawn from the study findings.

4.0 CONCLUSIONS

Implications for Practice

Because of the significant advances in treatment, survivorship has increased in the population with metastatic disease. As the treatments are mainly palliative in nature [84], gaining quality of life becomes a most significant target. This study shows that physical exercise is safe and may improve body composition, QoL, treatment toxicity and survival in metastatic cancer patients, including breast cancer [84-86].

Implications for research

Women with metastatic disease have historically been excluded from lifestyle interventions as they will eventually succumb to the disease [84]. However, it is evident from the growing number of survivors that there are indications that physical exercise and nutrition interventions can improve their wellbeing and outcomes. Body composition, weight and muscle strength are significant prognostic factors [45, 87] and the lack of research in the area indicates that more studies are needed to provide best practice advice to these women. It is not known what dosage and type of physical exercise and nutrition supplementation are necessary for achieving the best possible body composition and maintaining it for as long as possible. For example, how often should it be done, which exercises are best, what mode should be used, is home-based or group exercises more effective than supervised exercise interventions? What is the role of telehealth in this space? The best nutritional management of the disease, for example, supplementation, protein and omega-3 fatty acids, needs to be investigated to indicate effective dosage and timing.

For future studies, further work is needed regarding conducting high-quality RCTs with robust study designs that encompass larger sample sizes with high statistical power. Studies should incorporate appropriate intervention and comparison groups to accurately determine the most effective parameters of physical exercise and nutrition to achieve the desired outcome measures. Consensus also needs to be attained regarding the most appropriate types of exercise and standard measures of reporting to enable meta-analysis. Another topic that this review has brought to light is the issue of blinding of the observers by using independent data analysts and longer follow-up of the participants. Most significantly, there were no studies that looked at body composition. Additionally, there were no RCTs or observational studies that included both physical exercise and nutrition interventions. It is not known if the combination of both these variables would increase the ability of these patients to manage body composition and thus achieve better quality of life for longer.

These recommendations are based on ideal world considerations, however, there are practical, ethical and financial challenges involved in conducting studies with, for example, large sample sizes in this vulnerable population. Consequently, researchers could use the model of the Block Institute and appraise the efficacy of interventions with comparative groups in published studies. Alternatively, with the rise in popularity of telehealth, this is an avenue that could be explored to reduce burden and cost on these patients and possibly reduce study dropouts. Innovative thinking is required to overcome the hurdles and provide practitioners with evidence-based guidance, and this growing population of women the best opportunity to enjoy good quality of life for the time they do have.

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APPENDICES

Appendix 1

Common Diagnostic Tests

X-ray	**Used to detect changes in the bones or chest that may be caused by cancer**
Bone scan	A bone scan can pick up small areas in the bones where cells are growing more quickly. These are called 'hot spots'.
Blood tests	Blood tests can be used to for several checks things, including liver function, how healthy the bone marrow is and calcium levels in the blood.
Ultrasound	This may be used to look for changes in the liver and elsewhere in the body
Computed tomography **(CT / CAT scan)**	A CT scan may be used to look for cancer in different parts of the body.
Magnetic resonance imaging (MRI)	An MRI scan may be used to check for signs of cancer in the brain, spinal cord or spine. It may also be used to look for cancer in the liver.
Position emission tomography **(PET scan)**	A PET scan may be recommended to look for metastatic cancer. The scan can show any areas in the body where cells are more active than usual (e.g. fast-growing cancer cells).
Breast biopsy	The breast biopsy is done to confirm the diagnosis and find out what receptors are on the breast cancer cells. This information will help doctors work out which treatments are best.

[88]

Appendix 2

Final Search Terms

Search conducted October 25, 2017

Pubmed

("Stage IV"[tiab] OR metasta*[tiab] OR "secondary"[tiab] or "Stage four"[tiab])

AND

(((Breast[tiab] OR Mammalia*[tiab]) AND (Malignan*[tiab] OR Neoplas*[tiab] OR Tumor*[tiab] OR cancer*[tiab] OR tumour*[tiab] OR carcinoma*[tiab]))
OR "Breast Neoplasms"[Mesh])
AND

((((Protein[tiab] OR "amino acid" [tiab]) AND (supplement*[tiab])) OR nutrition*[tiab] OR diet*[tiab] OR *food*[tiab] *OR nutritive*[tiab] *OR "Fatty Acid"* [tiab] *OR "Fatty Acids"*[tiab] *OR "fatty acids, omega-3"[MeSH] OR "Fish Oils"[Mesh] OR "Fish Oil"*[tiab] *OR "Fish Oils"*[tiab] *OR "omega 3"*[tiab] OR "n-3 fatty acid"[tiab] OR "n3 fatty acid"[tiab] *OR "n3-fatty acids"*[tiab] *OR "n-3 fatty acids"*[tiab] OR "n-3 PUFA"[tiab] OR "n3 PUFA"[tiab] OR "n-3 polyunsaturated"[tiab] OR "n3 polyunsaturated"[tiab] OR "n3 poly unsaturated"[tiab] OR "n-3 poly unsaturated"[tiab] OR "seal oil"[tiab] OR "krill oil"[tiab] OR "cod oil"[tiab] OR Eicosapentaenoic Acid*[tiab] OR Docosahexaenoic acid*[tiab]) OR

("Physical activity"[tiab] OR "exercise movement techniques"[Mesh] OR "resistance training"[tiab] OR cardiovascular[tiab] OR exercise[tiab] OR Yoga[tiab] OR pilates[tiab] OR hydrotherapy[tiab] OR aerobic*[tiab] OR "Exercise Therapy"[Mesh] OR "Resistance Training"[Mesh]))

AND

(therapy[tiab] OR therapeutic[tiab] OR support[tiab] OR program*[tiab] OR intervention[tiab])

CINAHL

("Stage IV" OR metasta* OR "secondary" or "Stage four" OR MH "Neoplasm Metastasis+")

AND

(((Breast OR Mammalia* OR MH "Breast+")

AND

(Malignan* OR Neoplas* OR Tumor* OR cancer* OR tumour* OR carcinoma* OR MH "Neoplasms+") OR MH "Breast Neoplasms+")

AND

((((Protein OR "amino acid") AND (supplement*)) OR nutrition* OR diet* OR food OR nutritive OR MH "Fatty Acids, Omega-3+" OR MH "Fish Oils+" OR *"Fatty Acid" OR "Fatty Acids" OR "Fish Oil" OR "Fish Oils" OR "omega 3"* OR "n-3 fatty acid" OR "n3 fatty acid" *OR "n3-fatty acids" OR "n-3 fatty acids"* OR "n-3 PUFA" OR "n3 PUFA" OR "n-3 polyunsaturated" OR "n3 polyunsaturated" OR "n3 poly

unsaturated" OR "n-3 poly unsaturated" OR "seal oil" OR "krill oil" OR "cod oil" OR Eicosapentaenoic Acid* OR Docosahexaenoic acid*) OR

("Physical activity" OR MH "Exercise+" OR "resistance training" OR cardiovascular OR exercise OR Yoga OR pilates OR hydrotherapy OR aerobic* OR MH "Therapeutic Exercise+"))

AND

(therapy OR therapeutic OR support OR program* OR intervention*)

EMBASE

("Stage IV":ti,ab OR metasta*:ti,ab OR "secondary":ti,ab or "Stage four":ti,ab OR 'metastasis'/exp)

AND

(((Breast:ti,ab OR Mammalia*:ti,ab OR 'breast'/exp)

AND

(Malignan*:ti,ab OR Neoplas*:ti,ab OR Tumor*:ti,ab OR cancer*:ti,ab OR tumour*:ti,ab OR carcinoma*:ti,ab OR 'neoplasm'/exp)) OR 'breast cancer'/exp)

AND

((((Protein:ti,ab OR "amino acid":ti,ab) AND (supplement*:ti,ab)) OR nutrition*:ti,ab OR diet*:ti,ab OR food:ti,ab OR nutritive:ti,ab OR 'omega 3 fatty acid'/exp OR 'fish oil'/exp *OR "Fatty Acid"*:ti,ab *OR "Fatty Acids"*:ti,ab *OR "Fish Oil"*:ti,ab *OR "Fish Oils"*:ti,ab *OR "omega 3"*:ti,ab OR "n-3 fatty acid":ti,ab OR "n3 fatty acid":ti,ab *OR "n3-fatty acids"*:ti,ab *OR "n-3 fatty acids"*:ti,ab OR "n-3 PUFA":ti,ab OR "n3 PUFA":ti,ab OR "n-3 polyunsaturated":ti,ab OR "n3 polyunsaturated":ti,ab OR "n3 poly unsaturated":ti,ab OR "n-3 poly unsaturated":ti,ab OR "seal oil":ti,ab OR "krill oil":ti,ab OR "cod oil":ti,ab OR "Eicosapentaenoic Acid*":ti,ab OR "Docosahexaenoic acid*":ti,ab) OR

("Physical activity":ti,ab OR 'exercise'/exp OR "resistance training":ti,ab OR cardiovascular:ti,ab OR exercise:ti,ab OR Yoga:ti,ab OR pilates:ti,ab OR hydrotherapy:ti,ab OR aerobic*:ti,ab))

AND

(therapy:ti,ab OR therapeutic:ti,ab OR support:ti,ab OR program*:ti,ab OR intervention*:ti,ab)

Cochrane Central Database

("Stage IV" OR metasta* OR secondary OR "Stage four")

AND
(((Breast OR Mammalia*) AND (Malignan* OR Neoplas* OR Tumor* OR cancer* OR tumour* OR carcinoma*)) OR [mh "Breast Neoplasms"])
AND
((((Protein OR "amino acid") AND (supplement*)) OR nutrition* OR diet* OR food OR nutritive OR [mh "Fatty Acids, Omega-3"] OR [mh "fish oil"] OR *"Fatty Acid" OR "Fatty Acids" OR "Fish Oil" OR "Fish Oils" OR "omega 3"* OR "n-3 fatty acid" OR "n3 fatty acid" *OR "n3-fatty acids" OR "n-3 fatty acids"* OR "n-3 PUFA" OR "n3 PUFA" OR "n-3 polyunsaturated" OR "n3 polyunsaturated" OR "n3 poly

unsaturated" OR "n-3 poly unsaturated" OR "seal oil" OR "krill oil" OR "cod oil" OR Eicosapentaenoic Acid* OR Docosahexaenoic acid*)

OR

("Physical activity" OR [mh "exercise movement techniques"] OR "resistance training" OR cardiovascular OR exercise OR Yoga OR pilates OR hydrotherapy OR aerobic* OR [mh "Exercise Therapy"] OR [mh "Resistance Training"])) AND
(therapy OR therapeutic OR support OR program* OR intervention)

Appendix 3

Summary Table - Stages of Breast Cancer

Stage	Description
Stage 0	Stage 0 is used to describe non-invasive breast cancers, such as DCIS (ductal carcinoma in situ). There is no evidence of cancer cells or non-cancerous abnormal cells breaking out of the part of the breast in which they started, or getting through to or invading neighboring normal tissue.
Stage I **(includes subcategories IA or IB)**	Stage I describes invasive breast cancer (cancer cells are breaking through to or invading normal surrounding breast tissue) Microscopic invasion is possible in stage I breast cancer. In microscopic invasion, the cancer cells have just started to invade the tissue outside the lining of the duct or lobule, but the invading cancer cells can't measure more than 1 millimeter.
Stage II **(includes subcategories IIA or IIB)**	***Stage IIA describes invasive breast cancer in which:*** no tumor can be found in the breast, but cancer (larger than 2 millimeters) is found in 1 to 3 axillary lymph nodes (the lymph nodes under the arm) or in the lymph nodes near the breast bone (found during a sentinel node biopsy) OR the tumor is larger than 2 centimeters but not larger than 5 centimeters and has not spread to the axillary lymph nodes ***Stage IIB describes invasive breast cancer in which:*** the tumor is larger than 2 centimeters but no larger than 5 centimeters; small groups of breast cancer cells -- larger than 0.2 millimeter but not larger than 2 millimeters -- are found in the lymph nodes or lymph nodes near the breastbone the tumor is larger than 5 centimeters but has not spread to the axillary lymph nodes
Stage III **(includes subcategories IIIA, IIIB or IIIC)**	Stage III is divided into subcategories known as IIIA, IIIB, and IIIC. ***Stage IIIA describes invasive breast cancer in which either:*** no tumor is found in the breast or the tumor may be any size; cancer is found in 4 to 9 axillary lymph nodes or in the lymph nodes near the breastbone (found during imaging tests or a physical exam) OR the tumor is larger than 5 centimeters; cancer has spread to 1 to 3 axillary lymph nodes or to the lymph nodes near the breastbone (found during a sentinel lymph node biopsy)

	Stage IIIB describes invasive breast cancer in which: the tumor may be any size and has spread to the chest wall and/or skin of the breast and caused swelling or an ulcer AND may have spread to up to 9 axillary lymph nodes OR may have spread to lymph nodes near the breastbone Inflammatory breast cancer is considered at least stage IIIB. Typical features of inflammatory breast cancer and cancer cells have spread to the lymph nodes and may be found in the skin ***Stage IIIC describes invasive breast cancer in which:*** there may be no sign of cancer in the breast or, if there is a tumor, it may be any size and may have spread to the chest wall and/or the skin of the breast AND the cancer has spread to 10 or more axillary lymph nodes OR the cancer has spread to lymph nodes above or below the collarbone OR the cancer has spread to axillary lymph nodes or to lymph nodes near the breastbone
Stage IV	Stage IV describes invasive breast cancer that has spread beyond the breast and nearby lymph nodes to other organs of the body, such as the lungs, distant lymph nodes, skin, bones, liver, or brain. You may hear the words “advanced” and “metastatic” used to describe stage IV breast cancer. Cancer may be stage IV at first diagnosis or it can be a recurrence of a previous breast cancer that has spread to other parts of the body.

[89]

Appendix 4

Prospero Registration

Van: CRD-REGISTER <irss505@york.ac.uk>
Datum: 7 December 2017 om 00:36:10 GMT+10
Aan: "bvanderm@bond.edu.au" <bvanderm@bond.edu.au>
Onderwerp: PROSPERO Registration message [80412]
Antwoord aan: crd-register irss505@york.ac.uk

Dear Dr. van der Meij,

Thank you for submitting details of your systematic review "Systematic review of the effects of physical exercise and/or nutrition interventions on women with metastatic breast cancer" to the PROSPERO register. We are pleased to confirm that the record will be published within the next hour.

Your registration number is: CRD42017080412

As your review progresses, please update field #28 (strategy for data synthesis) with the structure of your meta-analysis when this becomes established.

You are free to update the record at any time, all submitted changes will be displayed as the latest version with previous versions available to public view. Please also give brief details of the key changes in the Revision notes facility. You can log in to PROSPERO and access your records at https://www.crd.york.ac.uk/PROSPERO

Comments and feedback on your experience of registering with PROSPERO are welcome at: crd-register@york.ac.uk

Best wishes for the successful completion of your review.

Yours sincerely,
PROSPERO Administrator
Centre for Reviews and Dissemination
University of York
York YO10 5DD
t: +44 (0) 1904 321049
e: CRD-register@york.ac.uk
www.york.ac.uk/inst/crd

Appendix 5

Downs and Black Assessment Tool

Appendix

Checklist for measuring study quality

Reporting

1. *Is the hypothesis/aim/objective of the study clearly described?*

yes	1
no	0

2. *Are the main outcomes to be measured clearly described in the Introduction or Methods section?*
If the main outcomes are first mentioned in the Results section, the question should be answered no.

yes	1
no	0

3. *Are the characteristics of the patients included in the study clearly described ?*
In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.

yes	1
no	0

4. *Are the interventions of interest clearly described?*
Treatments and placebo (where relevant) that are to be compared should be clearly described.

yes	1
no	0

5. *Are the distributions of principal confounders in each group of subjects to be compared clearly described?*
A list of principal confounders is provided.

yes	2
partially	1
no	0

6. *Are the main findings of the study clearly described?*
Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).

yes	1
no	0

7. *Does the study provide estimates of the random variability in the data for the main outcomes?*
In non normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.

yes	1
no	0

8. *Have all important adverse events that may be a consequence of the intervention been reported?*
This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).

yes	1
no	0

9. *Have the characteristics of patients lost to follow-up been described?*
This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.

yes	1
no	0

10. *Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*

yes	1
no	0

External validity

All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.

11. *Were the subjects asked to participate in the study representative of the entire population from which they were recruited?*
The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant

population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

yes	1
no	0
unable to determine	0

12. *Were those subjects who were prepared to participate representative of the entire population from which they were recruited?*
The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

yes	1
no	0
unable to determine	0

13. *Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?*
For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.

yes	1
no	0
unable to determine	0

Internal validity - bias

14. *Was an attempt made to blind study subjects to the intervention they have received ?*
For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

yes	1
no	0
unable to determine	0

15. *Was an attempt made to blind those measuring the main outcomes of the intervention?*

yes	1
no	0
unable to determine	0

16. *If any of the results of the study were based on "data dredging", was this made clear?*
Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.

yes	1
no	0
unable to determine	0

17. *In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls ?*
Where follow-up was the same for all study patients the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.

yes	1
no	0
unable to determine	0

18. *Were the statistical tests used to assess the main outcomes appropriate?*
The statistical techniques used must be appropriate to the data. For example non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

yes	1
no	0
unable to determine	0

19. *Was compliance with the intervention/s reliable?*
Where there was non compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.

yes	1
no	0
unable to determine	0

20. *Were the main outcome measures used accurate (valid and reliable)?*

For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.

yes	1
no	0
unable to determine	0

Internal validity - confounding (selection bias)

21. *Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?*
For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case-control studies where there is no information concerning the source of patients included in the study.

yes	1
no	0
unable to determine	0

22. *Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?*
For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

yes	1
no	0
unable to determine	0

23. *Were study subjects randomised to intervention groups?*
Studies which state that subjects wererandomised should be answered yes except where method of randomisation would not ensure random allocation. For example alternate allocation would score no because it is predictable.

yes	1
no	0
unable to determine	0

24. *Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?*
All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.

yes	1
no	0
unable to determine	0

25. *Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?*
This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non-randomised studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.

yes	1
no	0
unable to determine	0

26. *Were losses of patients to follow-up taken into account?*
If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.

yes	1
no	0
unable to determine	0

Power

27. *Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?*
Sample sizes have been calculated to detect a difference of x% and y%.

	Size of *smallest* intervention group	
A	$<n_1$	0
B	n_1–n_2	1
C	n_3–n_4	2
D	n_5–n_6	3
E	n_7–n_8	4
F	n_9+	5

Appendix 6

Journal of Supportive Care in Cancer – Author Instructions

TYPES OF PAPERS

Review Articles – generally solicited by the editors but unsolicited proposals containing an abstract and outline can be sent to the editors for consideration. The word limit for Review Articles is up to 4,000 words for body text (excludes figures, charts, references, abstract).

Methodological guidelines include

• PRISMA or MOOSE for systematic reviews and meta-analysis

TITLE PAGE

The title page should include:

The name(s) of the author(s)

A concise and informative title

The affiliation(s) and address(es) of the author(s)

The e-mail address, and telephone number(s) of the corresponding author. If available, the 16-digit ORCID of the author(s)

Abstract

Please provide an abstract of 150 to 250 words. The abstract should not contain any undefined abbreviations or unspecified references.

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

REVIEW PROCEDURE

All manuscripts undergo strict peer review. Manuscripts are initially considered by the Editor-in-Chief. Any manuscript that does not meet the general certain criteria of the journal, e.g.

• relevance to the aims of the journal with the topic being of overall general interest

• sufficiently original and contributing to the advancement of the field,

• clearly written with appropriate study methods, well-supported data and conclusions which are supported by the data will be returned to the author without review.

MANUSCRIPT PREPARATION

We urge authors to follow the guidelines for authors to speed up the review and publication process. All manuscripts are subject to copyediting upon acceptance, however, authors are asked to ensure that manuscripts from non-native English language speakers should have the language and grammar checked by a native speaker or a professional agency. Poorly written articles cannot be reviewed and will be returned to the authors.

Authorship Criteria and Contributions

All listed authors should have seen and approved the final version of the manuscript. All authors of accepted articles must sign an authorship form affirming that they have met all three of the following criteria for authorship, thereby accepting public responsibility for appropriate portions of the content:

1. substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;

2. drafting the article or revising it critically for important intellectual content;

3. approval of the version to be published and all subsequent versions.

Group members who are not authors should be listed in the Acknowledgment section of the manuscript as participating investigators. Individuals who do not meet the criteria for authorship but who have made substantial, direct contributions to the work (e.g., purely technical help, writing assistance, general or financial or material support) should be acknowledged in the Acknowledgments section of the manuscript, with a brief description of their contributions. Authors should obtain written permission from anyone they wish to list in the Acknowledgments section.

Redundant, Duplicate or Fraudulent Publication

Authors must not simultaneously submit their manuscripts to another publication if that manuscript is under consideration by Supportive Care in Cancer. Redundant or duplicate publication is a paper that overlaps substantially with one already published in print or electronic media. At the time of manuscript submission, authors must inform the editor about all submissions and previous publications that might be regarded as redundant or duplicate publication of the same or very similar work. Any such publication must be referred to and referenced in the new paper.

Copies of such material should be included with the submitted paper as a supplemental file.

TITLE PAGE

Title Page

The title page should include:

The name(s) of the author(s)

A concise and informative title

The affiliation(s) and address(es) of the author(s)

The e-mail address, and telephone number(s) of the corresponding author

If available, the 16-digit ORCID of the author(s)

Abstract

Please provide a structured abstract of 150 to 250 words which should be divided into the following sections:

Purpose (stating the main purposes and research question)

Methods

Results

Conclusions

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

STRUCTURED ABSTRACT

Authors are asked to state the relevance of their manuscript to inform research, policies and/or programs.

TEXT

Text Formatting

Manuscripts should be submitted in Word.

Use a normal, plain font (e.g., 10-point Times Roman) for text.

Use italics for emphasis.

Use the automatic page numbering function to number the pages.

Do not use field functions.

Use tab stops or other commands for indents, not the space bar.

Use the table function, not spreadsheets, to make tables.

Use the equation editor or Math Type for equations.

Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Headings

Please use no more than three levels of displayed headings.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data).

Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.